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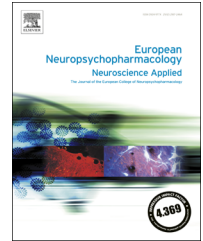
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# Stimulant treatment history predicts frontal-striatal structural connectivity in adolescents with attention-deficit/hyperactivity disorder

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Stimulant treatment

## Abstract

Diffusion tensor imaging (DTI) has revealed white matter abnormalities in individuals with attention-deficit/hyperactivity disorder (ADHD). Stimulant treatment may affect such abnormalities. The current study investigated associations between long-term stimulant treatment and white matter integrity within the frontal-striatal and mesolimbic pathways, in a large sample of children, adolescents and young adults with ADHD. Participants with ADHD ( $N=172$ ; mean age 17, range 9–26) underwent diffusion-weighted MRI scanning, along with an age- and gender-matched group of 96 control participants. Five study-specific white matter tract masks (orbitofrontal-striatal, orbitofrontal-amygdalar, amygdalar-striatal, dorsolateral-prefrontal-striatal and medialprefrontal-striatal) were created. First we analyzed case-control differences in fractional anisotropy (FA) and mean diffusivity (MD) within each tract. Second, FA and MD in each tract was predicted from cumulative stimulant intake within the ADHD group. After correction for multiple testing, participants with ADHD showed reduced FA in the orbitofrontal-striatal pathway ( $p=0.010$ , effect size=0.269). Within the ADHD group, higher cumulative stimulant intake was associated with lower MD in the same pathway ( $p=0.011$ , effect size=−0.164), but not with FA. The association between stimulant treatment and orbitofrontal-striatal MD was of modest effect size. It fell short of significance after adding

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ADHD severity or ADHD type to the model ( $p=0.036$  and  $p=0.094$ , respectively), while the effect size changed little. Our findings are compatible with stimulant treatment enhancing orbitofrontal-striatal white matter connectivity, and emphasize the importance of the orbitofrontal cortex and its connections in ADHD. Longitudinal studies including a drug-naïve baseline assessment are needed to distinguish between-subject variability in ADHD severity from treatment effects.

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## 1. Introduction

Diffusion tensor imaging (DTI) has revealed abnormalities in white matter integrity, or structural connectivity, in individuals with attention-deficit/hyperactivity disorder (ADHD) (for extensive reviews, see [Van Ewijk et al., 2012](#); [Konrad and Eickhoff, 2010](#)). Multiple parameters of white matter integrity can be derived from DTI, including fractional anisotropy (FA) and mean diffusivity (MD). FA measures directionality of water diffusion and is typically high in organized structures such as densely packed white matter bundles, as water is more likely to diffuse along the axons rather than perpendicular to the axons. MD measures the amount of water diffusion in any direction and is high in areas with few natural barriers to water diffusion, such as the ventricles. Less commonly reported are axial diffusivity (AD; measuring water diffusion along the main diffusion direction) and radial diffusivity (RD; measuring water diffusion perpendicular to the main diffusion direction). It is important to note that the interpretation of altered diffusion parameters is complex, especially in psychiatric disorders where changes are mostly subtle. Increased MD and decreased FA are often regarded as indications of impaired or decreased structural connectivity ([Thomason and Thompson, 2011](#)), but the neuro-pathological processes underlying such changes are largely unknown ([Jones et al., 2013](#)).

To date, findings on structural connectivity in individuals with ADHD compared to healthy controls have been mixed. Whereas some studies reported decreased FA and/or increased MD in individuals with ADHD compared to controls ([Ashtari et al., 2005](#); [Cao et al., 2010](#); [Hamilton et al., 2008](#); [Pavuluri et al., 2009](#)), suggesting decreased structural connectivity in ADHD, others found increased FA and/or decreased MD ([Li et al., 2010](#); [Peterson et al., 2011](#); [Silk et al., 2009b](#)). Null findings of no changes in structural connectivity have also been reported ([Silk et al., 2009a, 2009b](#)). In recent work from our group, van Ewijk et al. found widespread FA reduction in both participants with ADHD and their unaffected siblings, compared to healthy control participants, suggesting that reduced FA may represent a genetic vulnerability to ADHD. In addition, higher FA and lower MD were observed in more severely affected compared to less severely affected individuals with ADHD, which may reflect a second, distinct, mechanism associated with ADHD symptom severity ([Van Ewijk et al., 2014](#)). Inconsistent findings in previous studies may partially be explained by these two seemingly opposing mechanisms being at play.

Inconsistent findings may also reflect differences between the ADHD samples with regard to stimulant treatment history. Individuals with ADHD often take stimulants for prolonged periods of time. Studies investigating long-

term stimulant treatment effects on brain structure have almost exclusively focused on gray matter and/or subcortical structures. Several such studies (but not all) have suggested structural normalization with long-term stimulant treatment ([Nakao et al., 2011](#); [Shaw et al., 2009](#); [Sobel et al., 2010](#)), i.e. abnormalities typically associated with ADHD were smaller or absent in individuals with ADHD who had been treated with stimulants. Stimulant-induced changes in gray matter might be accompanied by changes in white matter.

Only few studies have explored long-term stimulant effects on white matter integrity quantified by DTI in individuals with ADHD. One study applied deterministic tractography to delineate the frontal-striatal tracts, and compared average FA within these tracts between children with a relatively short versus a relatively long history of stimulant treatment ([De Zeeuw et al., 2012](#)). No differences between the two groups were detected. Small sample size ( $n=13$  per group) and using average FA across all frontal-striatal tracts as the primary outcome measure limits the interpretation of this negative finding. A second study used both tract-based spatial statistics (TBSS) and whole-brain deterministic tractography, to perform a hypothesis-free search for differences in FA or MD between young treatment-naïve children with ADHD, children with ADHD who had been treated with stimulants, and healthy control children ( $n=16$ ,  $n=24$ , and  $n=26$ , respectively) ([De Luis-García et al., 2015](#)). Stimulant treatment was associated with decreased MD in several major white matter bundles, including the uncinate fasciculus connecting the medial temporal limbic structures to the orbitofrontal cortex. Importantly, differences in pre-treatment ADHD severity between children with and without stimulant treatment were not assessed, and may have confounded results. In a prior study of our own group on the association between structural connectivity and symptom severity, results did not change when history of stimulant treatment (treated/untreated) was taken into account ([Van Ewijk et al., 2014](#)).

In the current report, we investigated the association between stimulant treatment history and structural connectivity in a large sample of children, adolescents and young adults with ADHD. This investigation adds to the previous study from our group in two ways. First, in the current study we assessed stimulant treatment history to detail, and performed dimensional analyses of lifetime cumulative stimulant dose. Second, we applied a sensitive hypothesis-driven region-of-interest (ROI) approach based on the dopaminergic working mechanism of stimulants. Stimulants generate their clinical effects, at least partially,

by enhancing dopaminergic neurotransmission in the striatum (Volkow et al., 2012). Two major dopaminergic pathways connect the striatum to other brain regions: the frontal-striatal pathway, connecting the striatum to the medial and dorsolateral prefrontal cortex; and the meso-limbic pathway, connecting the striatum to the limbic system including the amygdala and orbitofrontal cortex. We used probabilistic tractography to quantify white matter microstructure within these pathways. A healthy control group was included for reference. We hypothesized that participants with ADHD would present with reduced FA and/or increased MD in frontal-striatal pathways, indicative of lower structural connectivity. Second, in line with observations of gray matter structural normalization with stimulant treatment, we hypothesized that FA would be higher and MD would be lower (both indicative of enhanced structural connectivity) in participants with a history of high cumulative stimulant intake, compared to those with a history of no or less stimulant intake.

## 2. Experimental procedures

### 2.1 Participants

An ADHD and control sample were selected from the NeuroIMAGE cohort, a family-based cohort that includes 415 families with one or more probands with ADHD, as well as 141 healthy control families (Von Rhein et al., 2014). For inclusion, participants had to meet the following criteria: (1) age between 8 and 30 years old, (2)  $IQ > 70$ , (3) no diagnosis of epilepsy, general learning difficulties, or known genetic disorders, and (4) availability of a good quality diffusion scan and T1 structural scan. Participants with ADHD had to meet diagnostic criteria for ADHD (see below). The following additional inclusion criteria applied to healthy control participants: (1) no past or present mental health care utilization, (2) no past or present psychiatric disorders (ADHD or otherwise) in first-degree relatives, and (3) no past or present psychoactive medication use reported by either the pharmacy or the participant/parents (incidental use was allowed). All subjects who did not fulfill criteria for either the ADHD or the control group were excluded, thus excluding unaffected siblings of individuals with ADHD. A group-matched (on age, gender, and scanner location) healthy control sample was drawn. The final sample consisted of 172 participants with ADHD and 96 healthy control participants (for reference), between the ages of nine and 26 years ( $M=17.2$ ,  $SD=3.1$ ). Informed consent was signed by all participants (parents signed informed consent for participants under 12 years of age) and their parents (for participants under 18 years of age), and the study was approved by the ethical committees of participating institutions.

### 2.2 Diagnostic assessment

All participants were assessed using a combination of a semi-structured diagnostic interview and Conners' ADHD questionnaires. For participants using medication, ratings of participants functioning were done off medication. All participants were administered the Dutch translation of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (Kaufman et al., 1997), carried out by trained professionals. Both the parents and the participant, if  $\geq 12$  years old, were interviewed separately and were initially administered the ADHD screening interview. Participants with elevated scores on any of the screening items were administered the full ADHD section. In addition, each participant was assessed with a parent-rated

questionnaire (Conners' Parent Rating Scale-Revised: Long version, Conners et al., 1998b) combined with either a teacher-rated questionnaire for children  $< 18$  years (Conners' Teacher Rating Scale-Revised: Long version; Conners et al., 1998a) or a self-report questionnaire for participants  $\geq 18$  years (Conners' Adult ADHD Rating Scales-Self-Report: Long version; Conners et al., 1999). Participants with  $\geq 6$  symptoms of hyperactive/impulsive behavior and/or inattentive behavior were diagnosed with ADHD, provided they: a) met the DSM-IV criteria for pervasiveness and impact of the disorder; b) had an onset-age before 12, and c) scored  $T \geq 63$  on at least one of the ADHD scales on either one of the Conners' ADHD questionnaires. Healthy control participants were required to score  $T < 63$  on each of the ADHD scales of each of the Conners' questionnaires, and have  $\leq 3$  combined symptoms. Criteria were adapted for participants of 18 years or older, such that five symptoms were sufficient for a diagnosis and  $\leq 2$  symptoms were allowed for healthy control participants. Additional assessments included the Children's Social Behavior Questionnaire (Hartman, et al., 2006) to measure symptoms of autism spectrum disorders, the block-design and vocabulary subtests of the Wechsler Intelligence Scale for Children (Wechsler, 2002) for participants  $< 18$ , or the Wechsler Adult Intelligence Scale (Wechsler, 2000) for participants  $\geq 18$  to estimate IQ, and the Children's Global Assessment Scale (Shaffer et al., 2014) to assess functional impairment in daily life.

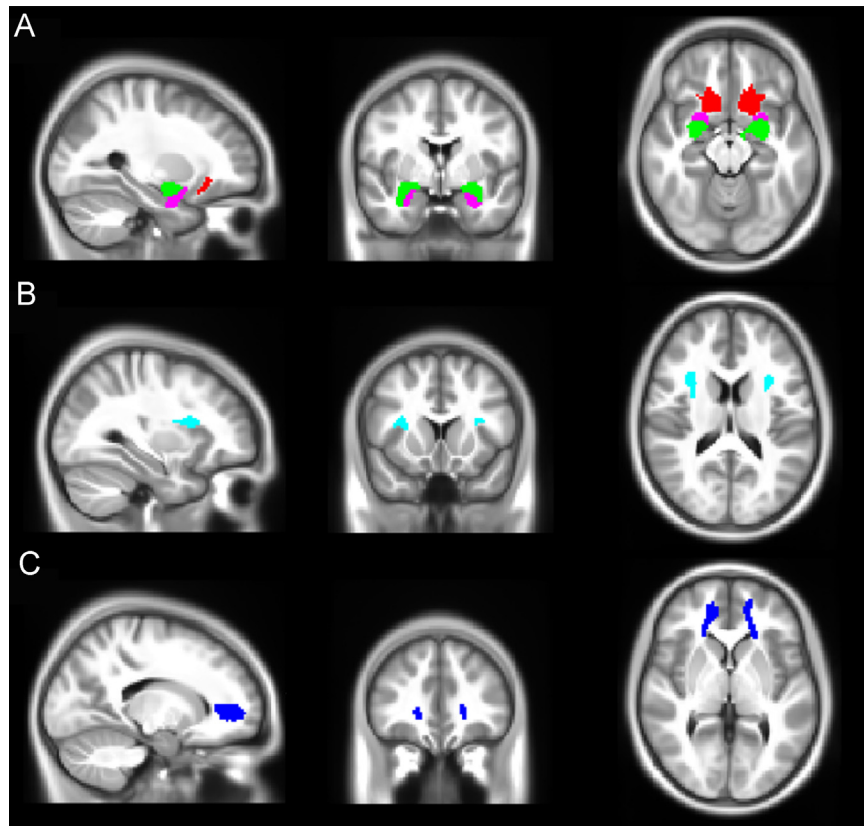
### 2.3 Assessment of medication history

All participants provided written consent to obtain lifetime medication transcripts from the pharmacy. For participants under the age of twelve, permission was obtained from one or both of the parents. In addition, an extensive questionnaire was used to assess lifetime history of psychoactive medication for all participants. The questionnaire was administered during the testing day, either by the parents or by the participant ( $> 18$ ). For healthy control participants, the pharmacy transcripts and questionnaires were used to ascertain a negative history of any type of psychoactive medication. For participants with ADHD, cumulative stimulant intake was calculated from the pharmacy transcripts as the lifetime total stimulant dose in mg. Dexamphetamine dose was multiplied by two in this calculation. If pharmacy transcripts did not cover the medicated period according to the medication questionnaire ( $n=48$ , 29%), stimulant intake during the missing period(s) were calculated from the questionnaire data, and were added to the cumulative intake derived from the pharmacy data. Cumulative stimulant intake was divided by participant's age minus 2.3 (the minimum stimulant start age within our sample), to obtain a measure of cumulative intake independent of age (CSI), which was used in all analyses.

### 2.4 MRI acquisition

Participants were asked to withhold use of psychoactive drugs for 48 h before scanning. MRI data was acquired at 1.5 T on a Siemens Sonata scanner at the VU Medical Center (Amsterdam, the Netherlands) and on a Siemens Avanto scanner at the Donders Center for Cognitive Neuroimaging, (Nijmegen, the Netherlands). An identical 8-channel phased array coil was used at both sites and all scan parameters were matched as closely as possible. The scan protocol included one eddy-current compensated diffusion-weighted SE-EPI sequence (5 volumes without directional weighting, followed by 60 diffusion-weighted volumes of 60 interleaved transverse slices each, slice thickness 2.2 mm, FOV=256 mm, TR=8500 ms, TE=97 ms;  $b$ -value=1000 s/mm<sup>2</sup>, GRAPPA-acceleration 2), and two T1-weighted MP-RAGE scans (TI=1000 ms, TR=2730 ms, TE=2.95 ms, FA=7°; 176 sagittal slices, voxel size  $1 \times 1 \times 1$  mm<sup>3</sup>, FOV=256  $\times$  256  $\times$  176 mm<sup>3</sup>; GRAPPA acceleration 2).





**Figure 1** Study-specific white matter tractography masks, projected on the study-specific standard brain template. Coordinates are in MNI-space. A. orbitofrontal-striatal tract (red), orbitofrontal-amygdalar tract (pink) and amygdalar-striatal tract (green;  $X = -26$ ,  $Y = 0$ ,  $Z = 14$ ) B. dorsolateral-prefrontal-striatal tract (light blue;  $X = 32$ ,  $Y = 14$ ,  $Z = 16$ ) C. medial-prefrontal-striatal tract (dark blue;  $X = -16$ ,  $Y = 36$ ,  $Z = 2$ ). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

## 2.5 MRI analyses

For each subject, residual eddy current correction and realignment of all denoised diffusion-weighted images per subject were performed in SPM8 (Wellcome Trust Center for Neuroimaging). Denoising was performed using a local PCA procedure and a dedicated robust estimation algorithm (PATCH; [Zwiers, 2010](#)) was used to correct for motion-induced artifacts and tensor estimation. Realignment parameters were comparable for participants with and without ADHD, indicating similar levels of motion-distortion in the two groups. B0 diffusion images of each participant were registered to their own T1 structural scan, which in turn was registered to the a 2 mm template (specific for NeuroIMAGE sample) using FNIRT in FSL, creating warp fields to transform images from subject space to standard space and vice versa.

First, the following masks were created from the AAL atlas in standard space: left and right dorsolateral prefrontal cortex (dlPFC; AAL 7+11+13 and 8+12+14), left and right medial prefrontal cortex (mPFC; AAL 23 and 24), left and right orbitofrontal cortex (OFC; AAL 5+9+15+25+27 and 6+10+16+26+28), left and right striatum (AAL 71+73 and 72+74), and left and right amygdala (AAL 41 and 42). Three additional exclusion masks were registered:  $X < -1$  (excluding the left hemisphere),  $X > 1$  (excluding the right hemisphere) and  $Y < -30$  (excluding all voxels posterior to the tail of the caudate nucleus). Next, all masks were inversely warped to subject space and used to specify in- and exclusion criteria for reconstructed white matter tracts. The probtrackx2 tool in FSL performed probabilistic tractography propagating 5000 streamlines per voxel within the seed mask, including all streams that reach the waypoint-mask, and excluding all streams

that ran through an exclusion-mask. The following white matter tracts were reconstructed for each hemisphere: dorsolateral-prefrontal-striatal (seed=dlPFC; waypoint=striatum), medial-prefrontal-striatal, (seed=mPFC; waypoint=striatum), orbitofrontal-striatal, (seed=OFC; waypoint=striatum), orbitofrontal-amygdalar (seed=amygdala; waypoint=OFC), and amygdalar-striatal (seed=amygdala; waypoint=striatum). All ROI-masks other than the seed- and waypoint-mask were specified as exclusion masks. Resulting distribution images were thresholded to include only voxels that were hit by at least 1% of all streamlines generated by probtrackx, and binarized to create a subject-specific mask of each white matter tract. These maps were then warped to standard space, summed up across all subjects, thresholded such that voxels were included if at least 75% of all subjects had a white matter tract in that voxel, and binarized to create a study-specific mask of each white matter tract in standard space ([Figure 1](#)). Last, FA and MD images of each participant were warped to standard space, and FA and MD within each tract-mask were extracted. For each tract we calculated left, right, and average FA and MD. For follow-up analyses we also warped axial diffusivity (AD) and radial diffusivity (RD) maps to standard space and extracted average AD and RD for each tract and participant.

## 2.6 Statistical analyses

Statistical analyses were performed in SPSS version 22.0.0.0 ([IBM, 2011](#)). First, we compared average FA and MD within each white matter tract between participants with ADHD and healthy control participants using General Linear Mixed (GLM) modeling, taking into account gender, scanner site, age, and age-squared and including a

random intercept to account for the clustered family data. We also examined possible interaction effects between diagnosis and age, age-squared, and gender. Second, the same statistical model was applied to investigate the effect of CSI on FA and MD (only within participants with ADHD), as well as possible interaction effects between CSI and age, age-squared, and gender. For the within-ADHD analyses, participants with missing stimulant treatment data ( $n=8$ ) were excluded, as well as one participant who was an outlier on cumulative stimulant intake ( $z=5.6$ ).

We applied a two-step method to correct for multiple comparisons. Given that we had five positively correlated tracts per DTI-measure, we first calculated the effective number of tests ( $M_{\text{eff}}$ ; Moskvinina and Schmidt, 2008) based on bivariate correlations between the five outcome measures (ranging from  $r=0.185$  to  $r=0.887$ ). Next,  $M_{\text{eff}}$  was applied to the Dunn-Sidak familywise error rate correction (Šidák, 1967). For the analyses of FA and MD,  $M_{\text{eff}}$ s were 3.81 and 3.40, and the adjusted alpha-levels derived from Dunn-Sidak-correction were 0.013 and 0.015, respectively.

Significant effects of treatment or diagnosis were ensued by follow-up analyses: (1) analyzing the left and right hemisphere separately, (2) analyzing AD and RD separately, and (3) adding to the model any clinical or demographic variable that was associated with CSI, as these may have been confounders (for treatment effects). The same adjusted alpha-levels were used in the follow-up analyses. Last, we tested the robustness of our findings by repeating our analyses within various subsamples, namely boys ( $n=172$ ) and girls ( $n=96$ ), participants who had been tested in Nijmegen ( $n=143$ ) and in Amsterdam ( $n=125$ ), participants with no history of dexamphetamine treatment ( $n=249$ ), and participants stratified into age quartiles ( $n_{<14.96}=67$ ,  $n_{14.96-17.50}=67$ ,  $n_{17.50-19.57}=68$ ,  $n_{>19.57}=66$ ; e-supplement I, available online).

### 3 Results

The ADHD and control samples did not differ in age (HC:  $M=16.96$ ,  $SD=3.26$ ; ADHD:  $M=17.39$ ,  $SD=3.05$ ;  $t=-1.096$ ,  $p=0.274$ ), gender (HC:  $N_{\text{MALE}}=56$ , 58%; ADHD:  $N_{\text{MALE}}=116$ , 67%;  $\chi^2=2.223$ ,  $p=0.136$ ), or scanner location (HC:  $N_{\text{NIJMEGEN}}=44$ , 46%; ADHD:  $N_{\text{NIJMEGEN}}=99$ , 58%;  $\chi^2=3.403$ ,  $p=0.065$ ). Participants with ADHD had lower IQ (HC:  $M=106.47$ ,  $SD=14.09$ ; ADHD:  $M=96.62$ ,  $SD=13.67$ ;  $t=5.582$ ;  $p=0.001$ ) compared to control participants. The difference in IQ was considered part of the ADHD phenotype (Dennis et al., 2009), thus IQ was not added as a covariate.

Cumulative stimulant intake was available for 163 participants with ADHD. Participants had inattentive type ( $n=82$ , 50%), combined type ( $n=66$ , 41%), or hyperactive type ADHD ( $n=15$ , 9%). Thirty-two percent ( $n=52$ ) had a comorbid diagnosis, mostly oppositional defiant disorder or conduct disorder ( $n=47$ , 29%), but also tic disorders ( $n=3$ , 2%) and anxiety/depression ( $n=4$ , 3%). Treatment characteristics of the ADHD group are summarized in Table 1. The vast majority had at some point in their lives been treated with stimulants, including immediate release methylphenidate ( $n=141$ , 87%), extended-release methylphenidate ( $n=112$ , 69%), and dexamphetamine ( $n=18$ , 11%). Average cumulative stimulant intake was 62,396 mg (equal to 5.7 years of 30 mg per day), ranging from zero mg (stimulant-naïve) to 289,000 mg (equal to 13.2 years of 60 mg per day). Forty percent ( $n=65$ ) of participants with ADHD had received stimulant treatment within three months prior to scanning; the other participants had ceased treatment prior to study participation. Psychoactive medication other than

stimulants was frequent, and included atomoxetine ( $n=20$ , 12%), atypical antipsychotics ( $n=22$ , 14%), benzodiazepines ( $n=10$ , 6%), and antidepressants ( $n=7$ , 4%). Individual differences in clinical characteristics or stimulant treatment history (other than CSI) were analyzed as potential confounders (see below).

### 3.1 Participants with ADHD vs. healthy control participants

Compared to healthy control participants, participants with ADHD had lower FA in white matter tracts connecting the striatum and the orbitofrontal cortex (Cohen's  $d=0.269$ ,  $p=0.010$ ). The direction of effect remained unchanged when participants were stratified by gender, scanner site, or age quartiles, and when participants treated with dexamphetamine preparations were excluded (e-Supplement I, available online). Follow-up analyses showed that lower OFC-striatal FA was present in both hemispheres, and significant after correction for multiple testing in the left hemisphere. There were no case-control differences in axial ( $p=0.132$ ) or radial diffusivity ( $p=0.218$ ) in this pathway. Lower FA in the dorsolateral-prefrontal-striatal pathway was nominally significant, but failed to reach the alpha-level adjusted for multiple testing (Cohen's  $d=0.289$ ,  $p=0.018$ ). In the mPFC-striatal tract, amygdalar-striatal tract, and the OFC-amygdalar tract we found no FA differences between participants with ADHD and healthy controls (Table 2). Further, we found no diagnosis-by-gender ( $p>0.432$ ), diagnosis-by-age ( $p>0.128$ ), or diagnosis-by-age-squared ( $p>0.289$ ) interaction effects on FA in any tract.

There were no between-group differences in MD in any of the tracts ( $p>0.503$ , Table 2). Moreover, we found no diagnosis-by-gender ( $p>0.142$ ), diagnosis-by-age ( $p>0.490$ ), or diagnosis-by-age-squared ( $p>0.186$ ) interaction effects on MD. Finally, across all participants, FA and MD were negatively

**Table 1** Treatment characteristics of the ADHD group ( $n=163$ ).

|  | N         | %         |
|--|-----------|-----------|
| Stimulant-naïve                            | 18        | 11        |
| Current users (< 3 months prior to scan)   | 65        | 40        |
| Other psychoactive medication (any)        | 40        | 25        |
|  | Mean      | SD        |
| Stimulant treatment duration (years)       | 4.31      | 3.39      |
| Stimulant age of initiation (years)*       | 8.66      | 2.63      |
| Stimulant age of cessation (years)†        | 12.79     | 5.78      |
| Stimulant cumulative stimulant intake (mg) | 62,395.95 | 55,929.65 |
| Stimulant mean daily dose (mg)             | 31.31     | 16.06     |

\*within participants who had received stimulant treatment ( $n=145$ ).

†within participants who had ceased treatment > 3 months prior to scanning ( $n=98$ ).

**Table 2** Main effects of diagnosis (ADHD or healthy control) on FA and MD for each tract.

|                     | FA       |          |      | MD       |          |      |
|---------------------|----------|----------|------|----------|----------|------|
|                     | <i>b</i> | <i>p</i> | Sign | <i>b</i> | <i>p</i> | Sign |
| OFC - Striatum      | 0.008    | 0.010    | **   | −0.001   | 0.876    |      |
| Right               | 0.008    | 0.032    | *    |          |          |      |
| Left                | 0.008    | 0.009    | **   |          |          |      |
| dLPFC - Striatum    | 0.008    | 0.018    | *    | < −0.001 | 0.951    |      |
| mPFC - Striatum     | < −0.001 | 0.912    |      | < −0.001 | 0.910    |      |
| Amygdala - Striatum | 0.004    | 0.253    |      | 0.001    | 0.880    |      |
| OFC - Amygdala      | 0.001    | 0.617    |      | 0.003    | 0.503    |      |

\**p* < 0.05;\*\*significant after correction for multiple testing,  $\alpha_{FA}=0.013$ ,  $\alpha_{MD}=0.015$ .Positive *b*-values indicate reduced FA/MD in participants with ADHD compared to healthy controls. Abbreviations: FA, fractional anisotropy; MD, mean diffusivity; OFC, orbitofrontal cortex; dLPFC, dorsolateral prefrontal cortex; mPFC, medial prefrontal cortex.**Table 3** Main effects of age-independent cumulative stimulant intake on FA and MD for each tract.

|                     | FA       |          |      | MD       |          |      |
|---------------------|----------|----------|------|----------|----------|------|
|                     | <i>b</i> | <i>p</i> | Sign | <i>b</i> | <i>p</i> | Sign |
| OFC - Striatum      | 0.001    | 0.501    |      | −0.005   | 0.011    | **   |
| Right               |          |          |      | −0.006   | 0.016    | *    |
| Left                |          |          |      | −0.004   | 0.027    | *    |
| mPFC - Striatum     | −0.001   | 0.713    |      | −0.005   | 0.021    | *    |
| OFC - Amygdala      | −0.001   | 0.389    |      | −0.005   | 0.016    | *    |
| dLPFC - Striatum    | 0.001    | 0.713    |      | −0.004   | 0.055    |      |
| Amygdala - Striatum | −0.002   | 0.355    |      | −0.003   | 0.119    |      |

\**p* < 0.05;\*\*significant after correction for multiple testing,  $\alpha_{FA}=0.013$ ,  $\alpha_{MD}=0.015$ .Positive *b*-values indicate reduced FA/MD in participants with ADHD compared to healthy controls. Abbreviations: FA, fractional anisotropy; MD, mean diffusivity; OFC, orbitofrontal cortex; dLPFC, dorsolateral prefrontal cortex; mPFC, medial prefrontal cortex.

correlated in the mPFC-striatal tract (Pearson's  $r = -0.212$ ,  $p < 0.001$ ), but not in the other tracts.

### 3.2 Cumulative stimulant treatment

Within the ADHD group, CSI did not predict FA values in any of the white matter tracts ( $p > 0.355$ , Table 3). Furthermore, there were no CSI-by-gender ( $p > 0.103$ ), CSI-by-age ( $p > 0.060$ ), or CSI-by-age-squared ( $p > 0.293$ ) interaction effects on FA. Cumulative stimulant intake was negatively associated with MD in orbitofrontal-striatal pathway (Cohen's  $d = -0.164$ ,  $p = 0.011$ ). The direction of effect remained unchanged when participants were stratified by gender, scanner site, or age quartiles, and when participants treated with dexamphetamine preparations were excluded (e-Supplement I, available online). Follow-up analyses revealed that higher CSI was associated with lower

MD in both hemispheres, and that higher CSI was associated with lower AD (Cohen's  $d = -0.107$ ,  $p = 0.046$ ) and lower RD (Cohen's  $d = -0.165$ ,  $p = 0.029$ ). None of the follow-up analyses reached the alpha-level adjusted for multiple testing ( $\alpha = 0.015$ ). In addition, we found nominally significant lower MD in the orbitofrontal-amygdalar (Cohen's  $d = -0.120$ ,  $p = 0.016$ ) and medial-prefrontal-striatal pathways (Cohen's  $d = -0.188$ ,  $p = 0.021$ ), but neither met the adjusted alpha-level. CSI was not associated with MD in the dLPFC-striatal or amygdalar-striatal tracts (Table 3). There were no CSI-by-gender interaction effects ( $p > 0.115$ ), CSI-by-age ( $p > 0.368$ ) or CSI-by-age-squared ( $p > 0.350$ ) interaction effects on MD. Within participants with ADHD, there was a negative correlation between FA and MD in the mPFC-striatal tract (Pearson's  $r = -0.211$ ,  $p = 0.007$ ), but not in the other tracts.

Cumulative stimulant intake was positively correlated with the number of ADHD symptoms ( $r = 0.271$ ,  $p = 0.001$ ), and was

different for the three ADHD types ( $F=8.380$ ,  $p=0.001$ ). CSI was higher in the combined type group compared to the hyperactive group ( $mean_{COMBINED}=14.6$ ,  $mean_{HYPERACTIVE}=5.9$ ,  $p=0.007$ ) and to the inattentive group ( $mean_{COMBINED}=14.6$ ,  $mean_{INATTENTIVE}=8.8$ ,  $p=0.002$ ). CSI was not related to functioning in daily life ( $p=0.325$ ), presence of co-morbid disorders ( $p=0.291$ ), treatment with non-stimulant ADHD medication ( $p=0.730$ ), treatment with medication other than for ADHD ( $p=0.206$ ), or symptoms of autism spectrum disorder ( $p=0.258$ ). The analyses of orbitofrontal-striatal MD were repeated including the number of ADHD symptoms as a covariate. Number of symptoms did not predict orbitofrontal-striatal MD ( $p=0.360$ ). Adding the number of symptoms to the model caused the effect of CSI to fall short of significance, although the size of the effect changed little (Cohen's  $d=-0.144$ ,  $p=0.036$ ). Similarly, ADHD type, added to the model as two dummy variables, did not predict OFC-striatal MD ( $p_{COMBINED\ vs.\ HYPERACTIVE}=0.090$ ;  $p_{COMBINED\ vs.\ INATTENTIVE}=0.109$ ), but adding this covariate caused the effect of CSI to fall short of significance (Cohen's  $d=-0.114$ ,  $p=0.094$ ). These analyses indicate that although ADHD severity, ADHD type, and stimulant exposure are overlapping (resulting in larger standard errors of the estimated regression coefficients when modeled simultaneously, reducing statistical significance), this overlap has little impact on the effect size of the association between orbitofrontal-striatal MD and CSI.

#### 4. Discussion

The current study investigated associations between stimulant treatment history and white matter microstructural abnormalities in frontal-striatal and mesolimbic pathways, in a large sample of children, adolescents, and young adults with ADHD. We had hypothesized that FA would be lower and MD would be higher, both indicative of impaired structural connectivity, in participants with ADHD compared to healthy control participants. Indeed we found lower FA in the orbitofrontal-striatal tracts in participants with ADHD. There were no case-control differences in MD. Second, we had hypothesized that white matter microstructural abnormalities would be more prominent in participants with ADHD who had received little or no stimulant treatment. We found that cumulative stimulant intake was negatively correlated with orbitofrontal-striatal MD, suggesting higher structural connectivity with more and/or longer stimulant treatment. We found no correlations between stimulant treatment and frontal-striatal or mesolimbic FA.

Our findings are in line with those of [De Luis-Garcia et al. \(2015\)](#), who found lower MD in children who had been treated with stimulants compared to those who had not. In their sample, lower MD in stimulant-treated children was present in white matter tracts connecting the orbitofrontal cortex, and this was not accompanied by higher FA. The interpretation of subtle FA and MD changes is equivocal. Increased MD and decreased FA may be regarded as indications of impaired structural connectivity, and often, but not always, co-occur ([Thomason and Thompson, 2011](#)). It remains speculative, however, which neurodevelopmental or neuropathological processes underlie such alterations in FA and MD ([Jones et al., 2013](#)). Changes in FA and MD in ADHD may represent two distinct mechanisms, i.e. reduced

FA may represent a familiar (e.g. genetic) vulnerability to ADHD, whereas MD may be a clinical state marker ([Van Ewijk et al., 2014](#)). The current associations between stimulant treatment and orbitofrontal-striatal MD but not FA are in line with this hypothesis. Alternatively, the discrepancy between FA and MD findings could suggest that stimulant treatment may interact with a non-dysfunctional feature of white matter connectivity. We wish to additionally emphasize that confirmation in an independent sample is needed to exclude the possibility of a Type 1 error thereby avoiding over-interpretation, especially given the modest effect size of the finding in MD.

Stimulant intake correlated with white matter abnormalities in pathways connecting the orbitofrontal cortex to the striatum, and, albeit only nominally significant, to the amygdala. Altered structural connectivity within orbitofrontal-striatal pathways in individuals with ADHD has been related to impulsivity ([Konrad et al., 2010](#)), impaired school functioning ([Wu et al., 2014](#)) and neuropsychological deficits ([Shang et al., 2013](#)). Very little is known about the long-term effects (multiple years) of stimulant treatment on either mesolimbic structures or on behaviors mediated by these structures. In previous studies of the current sample, we found no associations between stimulant treatment and striatal or amygdalar volumes ([Greven et al., 2015](#)) or orbitofrontal cortical thickness ([Schweren et al., 2015](#)). Other structural and functional neuroimaging studies, including a positron-emission tomography (PET) study, have indicated long-term stimulant treatment effects on the striatum and amygdala ([Ludolph et al., 2008](#); [Onnink et al., 2013](#)), but there have also been null findings ([Schlachtermeier et al., 2011](#); [Stoy et al., 2011](#)). Like the current study, each of these studies in adults has been observational and lacked pretreatment measurement. Nevertheless, previous studies in conjunction with the current study support the importance of the orbitofrontal cortex and its striatal and limbic connections in ADHD, and suggest that structural connectivity of the orbitofrontal cortex may be affected by stimulant treatment.

As we expected, stimulant treatment was positively associated with ADHD severity: participants with a history of higher cumulative stimulant intake presented with more ADHD symptoms compared to patients with little or no stimulant treatment history. Similarly, patients with different ADHD types presented with different treatment histories (i.e. higher stimulant intake in the combined group compared to the hyperactive and inattentive groups). Disentangling the individual contributions of stimulant treatment and ADHD severity or type is a challenge. Confounding by indication, where more severely affected individuals are likely to receive more treatment, is inevitable when studying long-term treatment effects in children. We attempted to address the confounding effect of clinical differences by entering ADHD severity and ADHD type as covariates in the model predicting MD from cumulative stimulant intake. These clinical variables were measured post-treatment, thus at best representing a proxy of pretreatment clinical differences. The treatment effect on orbitofrontal-striatal MD changed little when differences in ADHD severity and/or type were accounted for, i.e., the effect was small with and without these additional



covariates. However, the effect was no longer significant, which indicates an increased standard error around the estimated effect. When simultaneously analyzed, the effect of treatment was more significant than the effect of either of the clinical variables ( $p=0.036$  versus  $p=0.360$  for number of symptoms, and  $p=0.094$  versus  $p=0.134$  for ADHD type), which indicates that stimulant treatment history is an important predictor and more predictive than ADHD severity or type. In addition, when ADHD severity and type were each separately analyzed without cumulative stimulant intake, neither significantly predicted orbitofrontal-striatal MD (data not shown). We conclude that although confounding by indication cannot be excluded, our findings support the importance of stimulant treatment history for orbitofrontal-striatal MD.

The current study had the following limitations. Studies investigating long-term treatment effects in children, including the current study, are inevitably naturalistic by design. In addition our study lacked pre-treatment assessment. As a result, we cannot exclude the possibility that white matter differences may have led to stimulant prescription (possibly through more severe ADHD behavior) instead of vice versa. Second, some regions of our interest, including the orbitofrontal cortex, are relatively susceptible to DTI scanning artifacts (e.g. image distortion). Consequently, we used group templates of white matter tracts, as opposed to using each participant's individual tracts, which resulted in relatively small study-specific regions of interest per white matter tract. ROI selection of frontal-striatal pathways also precluded finding potential changes in other white matter pathways affected by non-dopaminergic stimulant effects. For example, noradrenergic stimulant effects are known to occur both within and beyond the PFC, and may result in white matter changes in the posterior lobes and cerebellum that were not studied here. Finally, performing tractography using masks of functionally defined striatal subregions (e.g., [Di Martino et al., 2008](#)) may in future studies enhance anatomical specificity of white matter tracts, and aid in understanding behavioral correlates of neural changes. There are several strengths to our study as well. This is the first study to date investigating long-term stimulant effects on white matter integrity in a large and representative ADHD sample. In addition, our sample with its wide age-range allowed the investigation of long-term treatment effects spanning multiple years. Moreover, using lifetime pharmacy transcripts stimulant treatment history was assessed to a level of detail that has not previously been achieved.

In conclusion, participants with ADHD showed white matter microstructural abnormalities in orbitofrontal-striatal pathways, and stimulant treatment was associated with white matter microstructure in this same pathway. Whereas stimulant treatment was related to MD, case-control differences were found in FA but not MD. These findings could be interpreted to suggest that differences in FA and MD may represent two distinct pathophysiological processes in ADHD, and/or that stimulant treatment may act through enhancing a non-dysfunctional feature of white matter connectivity. Both hypotheses need further investigation in independent samples. Our findings support the importance of the orbitofrontal cortex and its connections in the pathophysiology of ADHD.

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## Contributors

LJSS, CAH and PJH contributed to the conception of the study; LJSS, CAH, PJH, JO and JB contributed to the literature search and formation of hypotheses; LJSS and MPZ undertook the processing of MRI data; LJSS and CAH performed the statistical analyses; LJSS wrote the first draft of the manuscript; All authors contributed to the interpretation of the data and critical review of the manuscript; All authors have approved the final manuscript.

## Conflict of interest

LJS Schwenen, CA Hartman, MP Zwiers, D Heslenfeld and J Oosterlaan report no biomedical financial interest or potential conflicts of interest. Pieter Hoekstra has been a member of the advisory board of Shire and has received an unrestricted research grant from Shire. Barbara Franke has received a speaker fee from Merck. Jan Buitelaar has been in the past 3 years a consultant to / member of advisory board of / and/or speaker for Janssen Cilag BV, Eli Lilly, Shire, Novartis, Lundbeck and Servier. He is not an employee of any of these companies, nor a stock shareholder of any of these companies.

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## Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.euroneuro.2016.02.007>.

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